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Calibration and quality control materials[1])

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One of the prerequisites for the attainment of "accurate" analytical results in clinical chemistry is the use of suitable calibration materials and solutions. In addition, both precision and accuracy must be monitored using suitable control specimens which are independent of the calibration materials used. The differences between calibration materials and control materials are pointed out. Those characteristics are described which are of importance in calibration materials and control materials if these materials are to serve their purpose well. These characteristics are summarized at the end of the paper, and they represent the minimal information that the manufacturer should provide with his calibration and control materials. We have reached a stage where it is important to decide which of these characteristics are important and to make recommendations for the provision of the necessary information.
However, we do not yet have enough experience to justify a final decision on how to quantify some of these characteristics or what the allowable limits should be.

Obwohl gut geleitete Laboratorien heute in der Lage sind, präzise klinisch-chemische Analysen zu machen, ist deren Richtigkeit und damit deren Vergleichbarkeit noch nicht überall mit hinreichender Sicherheit gewährleistet. Dies kann nur erreicht werden, wenn geeignete Standards und Standard-Lösungen für die Eichung zur Verfügung stehen. Außerdem müssen die Präzision und die Richtigkeit der Analysen ständig durch ein unabhängiges System der laborinternen und externen Qualitätskontrolle überwacht werden. Dazu werden geeignete Kontrollproben benötigt, deren Eigenschaften sich grundsätzlich von denen der Standards unterscheiden. Die notwendigen Eigenschaften der Standards, der Standard-Lösungen und der Kontrollproben werden ausführlich behandelt. Die notwendigen Merkmale der Standards und Kontrollproben werden am Ende des Beitrags zusammengestellt. Die Hersteller von Standards und Kontrollproben sollen die Benutzer über die Merkmale ihrer Produkte entsprechend dieser Zusammenstellung informieren. Es ist aber sicher verfrüht, wenn man schon jetzt die Merkmale und deren Meßgrößen einschließlich der zulässigen Grenzen festlegen wollte.

One of the goals of clinical chemical analysis is to attain "accurate results". As long-term collaborative surveys have shown (1, 2), a high level of precision can be attained when replicate determinations on the same control specimen are made in one laboratory. When the means of the results from the participating laboratories are compared, however, such a large range is observed that individual results from different laboratories can often be compared only to a limited degree or not at all (3).

Inaccuracy in analytical results may be due, among other things, to the standards used or to inadequate monitoring for deficiencies in the methods. The effects of the different specificity of different methods on the results of analysis must be taken into consideration. In order to attain accurate results it is essential that accurate standard materials and control specimens suitable for the recognition of procedural deficiencies be used. It is thus necessary to determine the essential characteristics of standards and control specimens and to reach agreement on how to measure them. In this working paper the most important characteristics of calibration and quality control materials are discussed. The presentation is based on information from the literature and on laboratory work done in West Germany over the last few years. The paper is, of course, meant to provide a basis for discussion.

At this point the official regulations governing calibration and quality control materials in the U.S. and in West Germany should be mentioned, for reference will be made to them repeatedly. In the U.S. these regulations are the *Tentative Standard* (1972) of the National Committee for Clinical Laboratory Standards (NCCLS) (4). Efforts to develop this standard go back to 1967. The Tentative Standard currently in use is being tried out for one year, after which it will be discussed and amended as necessary before being presented for final acceptance. In West Germany the regulations are called *Guidelines of the Medical Society of West Germany* (1971) (Richtlinien der westdeutschen Bundesärztekammer) (5). These Guidelines for statistical quality control and collaborative surveys in clinical chemistry were developed by the Medical Society of West Germany in connection with a new Cali-

[1]) Adapted from a paper presented at the *International Conference on Standardization of Diagnostic Materials,* sponsored by the *World Health Organization* and the *Center for Disease Control,* Atlanta, Georgia, USA, June 5–8, 1973.

bration Act (Eichgesetz, 1969) (6). The German Society for Clinical Chemistry was influential in the development of these Guidelines in terms of both theoretical and practical considerations. According to these Guidelines, for both internal control of accuracy and for collaborative surveys the approved values or analytical values of control specimens and the associated confidence intervals must be determined by approved reference laboratories[2]).

The determination of the approved values for almost all of the specimens used for monitoring accuracy which are available in West Germany is done by reference laboratories headed by members of the German Society for Clinical Chemistry. This is done at the request of the manufacturer by the Reference Commission of the Society. This Commission has selected standards and methods of analysis and worked out procedural details, and these are adhered to by both the reference laboratories and the manufacturers of control specimens.

Following these procedures, we have also carried out approved value determinations in collaboration with laboratories in Switzerland and Scandinavia, and the results have been very satisfactory. Discussions are now in progress with the associations of clinical chemistry and manufacturers in other European countries.

We are in an important phase of development, and the procedures in use must be adapted continually if full advantage is to be taken of new theoretical knowledge, new technology and experience gained in the laboratory.

In this paper the differences between those characteristics desired in calibration materials and those important in quality control materials are emphasized. First these characteristics are discussed separately and then summarized in list form. The material presented here can be regarded as a set of guidelines on the characteristics to be considered in the preparation of calibration and control materials. These guidelines should be changed as necessary to keep up with the state of the art. It is urged that no final decisions be made at this early stage about how to quantify these characteristics, and the need for and possibilities of intensive international cooperation in the gaining of experience about calibration and control materials are stressed.

In this way the guidelines can be improved upon continually.

Classification of Calibration and Quality Control Materials

Most methods of analysis in clinical chemistry are procedures of a relative nature, that is, the concentration of a given component in a specimen is determined by comparing the reading obtained for the specimen with the reading of a standard solution whose concentration is known.

There are no problems if the analytical method is specific and the concentrations of the standard solution are exactly what they should be. Unfortunately there are only a few absolutely specific analytical methods which are suitable for routine analysis, with the result that the components of the values obtained for standard solutions and for specimens can differ greatly (Table 1).

Tab. 1. Components of the results of analysis in clinical chemistry

	Standard S	Patient specimen P	Control specimen
1.	"true value"	"true value"	"true value"
2.		+ nonspecific component	+ nonspecific component
3.		± component due to deficiencies in procedure	± component due to deficiencies in procedure
4.		± disturbing factors in the specimen, e.g., medication	
Result of analysis	s_i	P_i	x_i or y_i.

The contents listed on a standard solution should, for all practical purposes, be the same as the "true value". In the specimens, in addition to the specific component in the value obtained there are also nonspecific components. These nonspecific components in the specimens from patients may be subject to great variation both within and between individuals. In addition, shortcomings in the analytical methods and disturbing factors, e. g., drugs and their metabolites, can influence the result either positively or negatively (7).

Standards

The prerequisite for accurate measurement is accurate knowledge of the concentration of the standard solution used. We differentiate (8) between two kinds of standards and the solutions made from them (Table 2). When so-called standard specimens are used many problems arise. By standard specimens we mean secondary standards which contain the same components as clinical specimens, that is, they contain nonspecific, sometimes unknown components.

Quality Control Materials

The purpose of statistical quality control is to control the whole analytical method (9). The control specimens used in quality control must therefore be independent of the standards used in analysis. For it is not permissable to measure something against itself.

The minimum program for quality control specified in the Guidelines includes the following points (Table 3).

[2]) For a detailed explanation of "approved values" see "What is Accuracy?" under "Control Specimens for Control of Accuracy".

Tab. 2. Standards and standard solutions

Standard or standard material is a substance of known purity which is used as the basis for a comparison of measurements in the determination of this substance or another substance in a specimen.	
Primary standard:	Primary standard solution:
Mass can be determined exactly by weighing the pure substance.	Standard solution of known concentration. Produced by weighing the primary standard and dissolving it in a suitable solvent.
Secondary standard:	Secondary standard solution:
Mass can be determined only by chemical analysis.	Standard solution produced by dissolving a secondary standard in a suitable solvent
	Standard specimen:
	A secondary standard which contains the same components as clinical specimens. In both, determination of concentration by chemical analysis.

Tab. 3. Minimum program for quality control according to the Guidelines of the Medical Society of West Germany

1. Quality control within the laboratory	
a) Precision control:	in each series of analyses, even if it consists of only one specimen
b) Control of accuracy:	in every 4th series of analyses at the least
2. External quality control	
Collaborative surveys:	must be conducted at least 3 times a year
	if participating laboratory meets standards of collaborative survey it receives a certificate valid for 12 months

Control specimens are required for all three parts of this minimum program for quality control. The characteristics of these control specimens for the control of precision, the control of accuracy and the collaborative surveys will be discussed below. We have divided the material according to the kinds of control necessary because the requirements made on the control specimens can be seen most clearly in this way.

There are three large groups of control specimens (Table 4). They differ in composition and in method of production. There are advantages and disadvantages in the use of the different kinds of control specimens, and these should be weighed against each other before one kind of specimen is selected.

A case in point is the determination of creatinine in serum using the *Jaffé* reaction. Our co-worker Dr. *Knoll* (10) investigated the development of color over time (Fig. 1). The abscissa represents the time following the mixing of the reagents, the ordinate the development of color, measured in mg/l of creatinine in the serum and calculated via the extinction of a primary standard which was read after 15 minutes.

Tab. 4. Kinds of control specimens

Kind	Examples
1. **Pure solutions**	
a) *like the primary standard solutions*	*Wootton* 1964 (31)
b) *solutions containing pure substances and pure albumin*	Boehringer Mannheim
2. **Liquid serum preparations**	
with addition of pure substances of kinds already present.	Dade, Asid, Behringwerke AG
3. **Lyophilized control specimens**	
which are reconstituted before use	
a) *Dialysed plasma or serum* with addition of substances of kinds already present.	Warner-Chilcott
b) *Serum preparations* with addition of substances of kinds already present.	Dade, Hyland
c) *Native serum or plasma*	

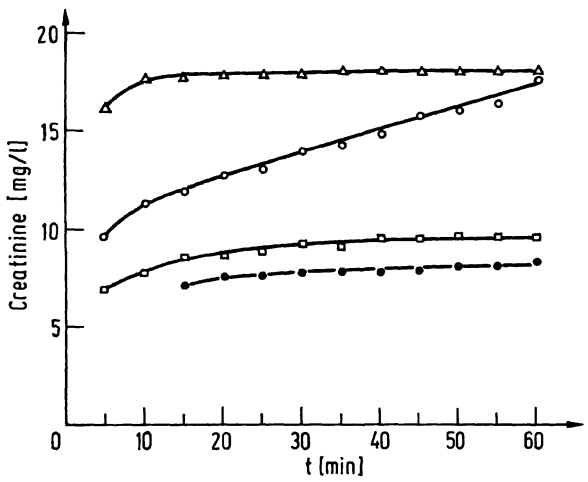

Fig. 1. The change in color over time in the *Jaffé* reaction for creatinine determination in various standards and control materials.
△——△ Primary standard
○——○ Lyophilized, reconstituted serum preparation
●——● Lyophilized, reconstituted serum preparation after specific adsorption on fuller's earth
□——□ Liquid serum preparation

With the *primary standard solution* the development of color is almost complete after 10 minutes; there is only a slight increase in extinction after this. But with *liquid serum preparations* the color continues to develop even after 20 minutes. The point in time when the photometric reading is made has an effect on the value obtained, and this may mean that the measurement is less precise. In lyophilized and reconstituted *serum preparations* the color development takes place even faster than in liquid control specimens and thus the time at which the reading is made has an even greater effect on the result. When we switched from a liquid to a lyophilized control specimen for the precision control of creatinine determinations a

number of years ago, we were horrified to find that our day-to-day precision became much worse. We spent a great deal of time trying to find the cause. In the end we developed a more specific procedure involving adsorption on fuller's earth and tested this procedure for reliability, including specificity. The development of color over time is about the same as for a primary standard solution. The conclusion can be drawn that the continuing increase in extinction in the control specimen is due to nonspecific components.
This observation is very instructive. The requirement must be made that the control specimen and the kind of material to be examined be as similar as possible because otherwise the disturbances in the measurement resulting from nonspecific components will not be recognized. With creatinine we trusted too long in an apparently high level of precision which, in fact, depended on the nature of the control specimen.

Broughton and *Annan* (11) showed recently that the day-to-day precision in the analysis of water-base control solutions is much better than in the analysis of solutions containing protein. *Skeggs* (12) found that in the Auto-Analyzer urea and glucose dialyse from water and from blood at different rates.
The conclusion must be drawn that we can only obtain realistic information on the reliability of our analyses if the control specimens used are as much like the clinical specimens as possible.

If the primary standard is used as the control specimen there are the following disadvantages:
1. The precision appears to be better than it really is.
2. Disturbances in the analysis due to nonspecific components in the specimens are not recognized. A much higher level of precision can be simulated with the control specimen than can be attained in the analysis of the clinical specimens.

Basic Requirements for Calibration and Quality Control Materials

1. Calibration materials, quality control materials and solutions made with them must be completely independent of one another.
2. There are basic differences in the composition desired for calibration solutions and quality control solutions.
   a) *Calibration Materials* should be as pure as possible, and solutions made using them should, ideally, consist of only the exactly weighed pure substance and a pure solvent, resulting in a *primary standard solution.*
   b) *Quality Control Materials* should be as much like the specimen to be examined as is practicable with respect to the type and concentration of both the main constituents and the other, nonspecific components. Only then is the effective control of reliability possible. Such a specimen is called a *control specimen.*

Characteristics of Calibration Materials

In this section the criteria for purity in calibration materials (13), the preparation of calibration solutions and the question of the stability of both calibration materials and solutions are discussed.

Primary Standard Materials

Primary standards should have the characteristics listed (14, 15) in Table 5.
The definitions of highly pure standard materials given by the International Union of Pure and Applied Chemistry (IUPAC) (16) are shown in Table 6.
In clinical chemistry it is difficult to find calibration materials which meet the IUPAC criteria: because the materials have a complicated structure it is difficult to purify and dry them. And for many of the materials

Tab. 5. Characteristics of primary standard (8)

1. It must be a stable substance of definite composition.
2. It must be a substance that can be dried in the course of preparation, preferably at 105–110°, without change in composition.
3. It should have a high equivalent weight in order that weighing errors may have a relatively small effect.
4. It must be a substance that can be accurately analyzed.

Tab. 6. IUPAC classification for high-purity material (17)

Grade A:	Atomic-weight standard
Grade B:	Ultimate standard a substance which can be purified to virtually atomic-weight standard
Grade C:	Primary standard a commercially available substance of purity 100 ± 0.02%
Grade D:	Working standard a commercially available substance of purity 100 ± 0.05%
Grade E:	Secondary standard a substance of lower purity, which can be standardized against primary (Grade C) material

Tab. 7. Standard reference materials for clinical measurements

SRM No.	Name	Purity, %
186Ic	Potassium dihydrogen phosphate	99.9
186IIc	Disodium hydrogen phosphate	99.9
911	Cholesterol	99.4
912	Urea	99.7
913	Uric acid	99.7
914	Creatinine	99.8
915	Calcium carbonate	99.9
916	Bilirubin	99
917	*D*-Glucose	99.9
918	Potassium chloride	99.9
922	tris(Hydroxymethyl)amino-methane	99.9
923	tris(Hydroxymethyl)amino-methane hydrochloride	99.7
2201	NaCl	99.9
2202	KCl	99.9

adequate criteria for purity have not yet been established. Over the last few years in the U.S. the National Bureau of Standards (NBS), continuing work begun by the American Association of Clinical Chemists, has developed criteria for the purity of a substantial number of calibration materials used in clinical chemistry (17, 18). Materials meeting these criteria are called Standard Reference Materials (SRM's) and can be purchased from the NBS (Table 7).
Because of the difficulties in purifying these structurally complicated and sensitive substances, only the inorganic SRM's available from the NBS meet the strict requirements of the IUPAC.
Clearly, the purity and its method of determination should be provided with each container of a calibration material. In the literature *Tietze* states a level of purity of 99.95% for primary standards. *Henry* states it should be 99.7%. It would be desirable for the manufacturers of calibration materials to provide detailed information on the purity of their products together with the analytical method used for the determination; this is done by E. Merck of Germany (19) and a few other companies (20). Wherever possible, the manufacturers should also compare their products with the SRM's of the NBS.

Secondary Standard

To determine the true content of secondary standards, reference methods in the narrowest sense of the term should be used. But since these are only rarely available (21), methods with proven specificity are the best alternative. Here it is emphasized that the secondary standards should contain only those constituents necessary for the calibration. The amount of nonspecific constituents in secondary standards should be kept to a minimum.
It is certainly inadmissable to use for calibration purposes control specimens with large amounts of nonspecific constituents which have been made up for control of accuracy. If standard specimens must be used, they should be prepared synthetically from pure crystallized albumin and other pure substances. These standard specimens must then be analysed.
Since this problem also arises in an analogous way in the determination of approved values for quality control materials, it will be discussed in that section.

Preparation of Standard Solutions

The preparation of standard solutions should be described in detail, including statements on the criteria for the purity of the calibration material, on drying procedures and on the purity of the solvent used.
The ideal primary standard solution can be put through the analytical procedure just as the natural specimen can. With hydrophobic substances, e. g., cholesterol (22, 23) and bilirubin (24), it may be difficult to prepare primary standard solutions which can be mixed with water.
The standards commissions of the national clinical chemistry societies should exchange information on their experience in the preparation of primary standard solutions; in those cases where no suitable regulations exist, the societies should cooperate to work out such regulations.

Stability of Standard Solutions

A careful study must be made of the stability of standard solutions when they are stored at room temperature. Those factors which influence the concentration measurably must be described and eliminated; an example is the effect of light on bilirubin. Special problems arise when the standard solutions are components in reagent kits and are subjected to great changes in temperature by being sent through the mail. The same guidelines hold here as for the shelf life of control specimens.

Characteristics of Quality Control Materials

The characteristics of the control specimens used are crucial to the effectiveness of statistical quality control. The manufacturers of control specimens should check them in their products before offering the products for sale and they should make their findings available to the users.
The characteristics of control specimens for precision control and the additional characteristics of control specimens to be used in controls of accuracy and in collaborative surveys are discussed.

Control Specimens for Precision Control

Origin of the Material

In order to be able to recognize the similarity of the control specimen and the clinical specimen, it is necessary to know the origin of the basic materials, e. g., human serum, bovine serum, bovine albumin. Information should also be available on the origin of components which are added. It is particularly important to know the origin of the enzyme activities added to those already present.
Additives: Information on additives such as antibiotics, chemical preservatives, coagulants and anticoagulants should be provided because of the possible effect these additives may have on the analysis.

Characteristics of the Containers

The interaction between specimens and containers, including the devices used for closing the containers, under normal storage conditions in a refrigerator and also under extreme conditions and in deep freezers should be investigated. At one point we observed that stoppers which had been stored for a long time in a freezer were no longer leakproof.

Concentration of the Components

The concentration of the components to be analyzed should not be in the middle of the normal range, as is to

be expected in a serum pool, but at the levels which are important for clinical decisions, for instance, near the upper limit of the normal range. For it is at this decision limit that the highest levels of precision and accuracy are required (25). For a few components, such as the transaminases, a measurement made at the upper limit of the normal range, in this case 16 U/l, is not very precise. Therefore, extraneous enzymes are used to attain a higher activity, for example, in the range of 30–40 U/l. At this level of activity the measurement itself is more precise, but the precision at the decision limit remains unchanged.

In addition, it is sometimes desirable to conduct controls on specimens with pathological concentrations. The concentrations should be chosen so that the specimens can be analysed without being diluted first, so that the precision of the measurement is tested at the upper level of the allowable range of measurement without the superimposition of the precision of dilution of the sample.

Intervial Variability

An important source of error can be intervial variability. This is due to a whole series of factors (Table 8). The user of a control specimen should be told to what degree the factors A and B may be present. He should receive detailed instructions on how to hold constant the influences resulting from factor B.

Tab. 8. Factors affecting intervial variability

A. Related to the Manufacturing Process
1. Homogeneity of the liquid material
2. Precision in the filling of containers
3. Moisture remaining after freeze-drying
4. Changes in components due to sterilization or lyophilization
B. Related to Reconstitution
1. Solubility of the components
2. Homogeneity of the solution
3. Turbidity
4. Precision of pipetting the solvent

The Tentative Standard, NCCLS, (1972) (4) requires that the intervial variation, expressed as a coefficient of variation, be less than or equal to ± 0.5% and that p be less than or equal to 1.0% for the 95% confidence limits.
In testing the intervial variability of lyophilized serum specimens to be used for control of precision, coefficients of variation of 0.59% and 13.8% were found by weighing for A2 and A3 (*P. M. G. Broughton,* personal communication 1971).
Considering these observations, it is essential that the manufacturers check the intervial variability continually and provide information on the results of their tests. From this information it is possible to judge what levels of precision from day-to-day can be detected with a given control specimen.

Shelf Life

By shelf life we mean the length of time that a control specimen can be stored as received from the manufacturer without any change in the concentration of any component. This aspect is of particular importance for precision control specimens, which are usually used over a period of many months. The length of time a precision control specimen can be used should be quite long because the change to another charge means a new preperiod of 20 working days. This preperiod is necessary to determine the control limits for the control chart.

1. *Liquid Control Specimens.* For liquid control specimens, the optimal conditions for storage should be stated and, in addition, information provided on the allowable limits, including time, when conditions are less than ideal, for example, when specimens are sent through the mail in summer. The manufacturers should state at least the expiration date under optimum storage conditions and for short-term storage under specified extreme conditions. If necessary, additional information should be provided about sensitive components. When we were looking for a systematic error in our determination of creatinine a number of years ago we found we had to assume that the measurable creatinine level in the control specimen had dropped. Upon inquiry the manufacturer confirmed this fact, which had been known to him for some time. The useful life of vials which have been opened is particularly affected by bacterial contamination, and so it cannot be discussed in general here.
2. *Lyophilized Control Specimens.* With lyophilized control specimens the shelf life of the specimen as sold and as reconstituted must be considered separately. The information provided on lyophilized specimens as sold should be the same as that requested above for liquid control specimens, and specific instructions for reconstituting the specimens should also be included. For reconstituted specimens the following points should be investigated and reported on: short-term storage up to 8 hours at room temperature, storage under refrigeration with temperature stated, and storage in a deep freezer (26, 27). In the latter case, additional information is needed on how often the specimen can be thawed and refrozen without any significant changes in concentration.

Control Specimens for Control of Accuracy

The same requirements should be made for these control specimens as for those used in precision control. But while precision can be controlled successfully, there are still a good number of unsolved problems regarding control of accuracy.

What is Accuracy?

There is agreement that the control of accuracy in connection with quality control should involve the analysis of an accuracy control specimen Y where the result of the analysis y_i is compared with the value $\bar{y}$ already de-

termined for the accuracy control specimen. No particular problems arise here if the analytical method used is completely specific. Then

$$\bar{y} = \mu_0 \text{ where } \mu_0 \text{ is the "true value".}$$

In this case accuracy (A) is (28)

$$A(\mu_0) = y_i - \mu_0.$$

We know, however, that in many routine methods the nonspecific components in the clinical specimens and the control specimens are also included. Beyond this, shortcomings in procedure can affect the results both positively and negatively. As a consequence, the mean values obtained using routine methods are often different from the "true value". We therefore call these means in German "Sollwerte" ($\bar{y}$)', which might be called "approved values" in English. These approved values are dependent on the method used. It is therefore necessary to include a detailed description of the method used and give a literature reference for the result of the test for specificity.

Then the test for accuracy made by comparison with an approved value would be

$$A(\bar{y}) = y_i - \bar{y}.$$

This means that when one speaks of the accuracy of analytical result one must specify whether the test was made by comparison with the "true value" (μ_0) or with the approved value ($\bar{y}$). If a routine method is completely specific then in the absence of systematic error it is possible that

$$A(\bar{y}) = A(\mu_0).$$

Since every analytical result is affected by chance errors, the confidence limits should be given for each approved value ($\bar{y}$). These confidence limits should be determined using the same standard deviation as that of the analytical result. The best standard deviation would be the precision from day to day of the individual result. Confidence limits at the 95% level should be required. It was on these considerations that the Standards Commission of the German Society for Clinical Chemistry based its determinations of approved values in connection with the German Calibration Act. The Commission proceeds as shown in Figure 2.

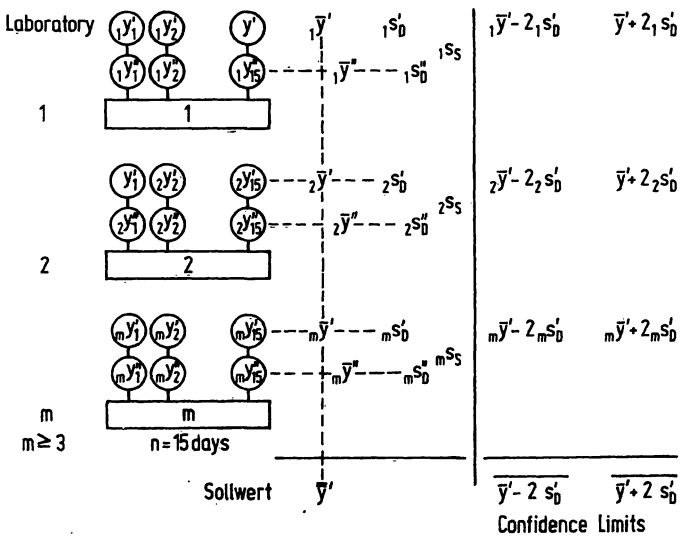

Fig. 2. Method for the determination of approved values used by the German Society for Clinical Chemistry.

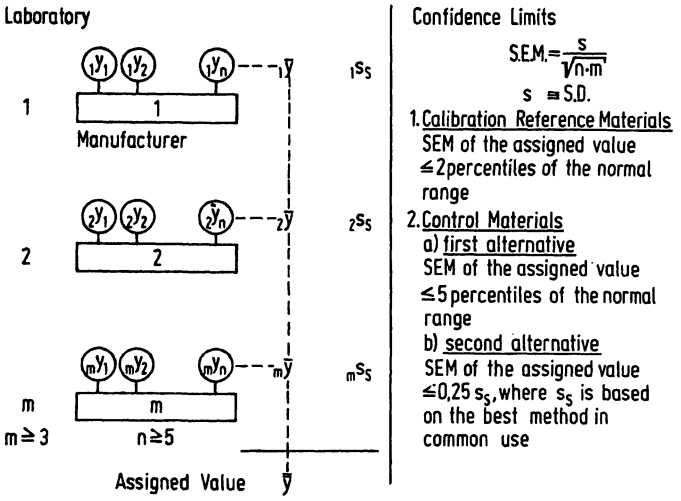

Fig. 3. Method for the determination of assigned values specified in the Tentative Standard of the NCCLS, USA.
m = Number of laboratories participating in the determination.
S. E. M. = standard error of the mean.

This procedure had been tested earlier in the Collaborative Survey of 1969 and had stood the test (2), as a comparison of data shows.

As compared to this, the Tentative Standard of the NCCLS in the United States recommends the procedure shown in Figure 3.

It seems to me to be a disadvantage that the confidence limits of the assigned value are not given along with the standard deviation of the individual result to be compared with it. The S.E.M. used for the data on the confidence limits can be varied greatly by the number of analyses included. Therefore the number of analyses on which the confidence limits of the assigned value are based should also be given; then the deviation of the individual result can be computed. If the approved values and their confidence limits determined using the German method are compared with the confidence limits of the assigned values determined according to the Tentative Standard of the NCCLS, it can be seen that almost all approved values meet the requirements for calibration reference materials.

In general it should be required that the manufacturers state not only the criterion for the position of the approved values they give but also the confidence limits of this criterion. Upon request they should also provide the experimental design for determining the approved value and the procedure used for the statistical evaluation of the approved value.

The determination of approved values for enzyme activities is particularly difficult because of the great number of test conditions and temperatures involved. In this case

it is absolutely essential that an international agreement on standardized conditions, such as we have already worked out for Germany (29, 30), be made soon.

List of Requests to the Manufacturers of Calibration and Quality Control Materials

Calibration and quality control materials can do the job required of them only if they have the characteristics discussed above. Knowledge of these characteristics is a prerequisite for the meaningful use of these materials. The characteristics listed below should be investigated by the manufacturers and information on them should be provided to the user on the information sheets sent with the products or be available on request. The list of characteristics should serve as a basis for discussion between manufacturer and user as they work together in an atmosphere of mutual trust on the development of better calibration and quality control materials.
However, since we are still at the stage of gaining experience about the theoretically desirable and experimentally feasible characteristics of calibration and quality control materials, no final decisions should be made yet in the form of laws or governmental regulations on how these characteristics should be quantified. Such agreements at this time would make it difficult to adapt quickly when experience shows us ways to provide better materials.

Calibration Materials

The following information should be provided or be available on request:

Statement of

1. Kind of standard (primary standard, secondary standard or standard specimen)

Primary Standards

2. Purity of the standard material, analogous to the information provided by the NBS
3. Where possible, comparison of the standard material with the SRM of the NBS
4. Method of preparation of standard solutions, in particular the kind and purity of the solvent; for mixtures, components and their purity
5. Shelf life in form received from manufacturer
   a) Under optimal conditions, which are specified in detail
   b) Under extreme conditions, which are specified in detail
   c) Expiration dates for a) and b).
6. Stability of standard solution after it has been opened
   a) When stored under refrigeration at 4–6° C after vial has been opened
   b) When stored at room temperature after vial has been opened
   c) Precautionary measures necessary
7. List of methods for which the standard can be used for calibration purposes. Warning about those methods for which it can only be used after certain precautionary measures have been taken or not be used at all.

Secondary Standards and Standard Specimens

8. See statements 7 to 9 under "Quality Control Materials"
9. The nonspecific components in the declared values are stated, including statement of analytical method employed.

Quality Control Materials

Statement of

1. Origin of basic material in control specimen
2. Origin and purity of any component added to the basic material
3. Intervial variability
4. Shelf life in form received from manufacturer
   a) Under optimal storage conditions
   b) Under extreme conditions, which are specified in detail
   c) Expiration date
5. Useful life of liquid control specimens after they have been opened
   a) When stored under refrigeration at 4–6° C after vial has been opened
   b) When stored at room temperature after vial has been opened.
6. For lyophilized control specimens a detailed description of how to reconstitute, including the waiting period necessary after reconstitution before the specimen can be used (of special importance for alkaline phosphatase)
7. Period of time control specimen can be used after reconstitution without change in concentration
   a) When stored under refrigeration at 4–6° C
   b) When stored at room temperature
   c) When stored in a deep freezer at -15° C, and number of times the specimen may be thawed and refrozen
8. Experimental design for the determination of approved values
   a) Number of laboratories
   b) Number of determinations in a series
   c) Number of series on different days
9. Methods used to determine the approved value
   a) Use reference method if possible
   b) For routine methods: literature references on the description and testing of the reliability of the methods, in particular their specificity
10. Statistical procedure used in the determination of the approved value
    a) Mean
    b) Criteria for variation

Conclusions and Recommendations

1. In many aspects of the development of calibration and control materials we are still at the stage of developing theoretical concepts and gaining experimental experience in the laboratory.
2. The main characteristics of the calibration materials and control materials and their importance are known. The manufacturers are requested to provide information on these characteristics, if necessary having conducted special tests first.
3. The national clinical chemistry societies should work with the manufacturers in the testing of these characteristics and in the determination of what requirements are desirable and feasible in terms of optimal diagnosis.
4. We cannot progress rapidly enough on the many urgent tasks facing us if we work only on a national level. Rather, coordinated international cooperation is necessary within the framework of the IFCC, its Committee on Standards and its Expert Panels. In Europe a step in this direction has already been made.
5. This paper is conceived of as a basis for discussion in the planning of such an international effort.
6. It seems too early for the fixing of standards. This should come after studies conducted on an international level have been evaluated.

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